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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/916,709	07/27/2001	Michael D. Doyle	001-1	8247

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EXAMINER	
SMITH, CAROLYN L	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 06/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/916,709	DOYLE ET AL.	
	Examiner	Art Unit	
	Carolyn L. Smith	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,7 and 9-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,7 and 9-11* is/are rejected.

7)☒ Claim(s) *4* is/are objected to.

8)☒ Claim(s) *1-4,6,7 and 9-11* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission, filed 4/6/05, has been entered.

Cancelled claims 5 and 8 and amended claims 1-4, 6-7, and 9-11, filed 4/6/05, are acknowledged.

Claims herein under examination are 1-4, 6-7, and 9-11.

Claim Objections

Claim 4 is objected to because of the following minor informality: The phrase "coordinate indices" (line 15) appears to be grammatically incorrect. It appears that a verb needs to be amended, such as ending it with "–ing" or some other sentence construction, in order to fit in with the remaining grammar of the providing step. Appropriate correction is requested.

Claims Rejected Under 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

LACK OF WRITTEN DESCRIPTION/NEW MATTER

Claims 1-3, 7, and 9-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time of the invention was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

Claim 1 recites the phrases "associating each incised section sample" (line 12), "unique set of indices" (lines 13-14), and "associated with the indexed incised section sample" (last two lines) which do not appear to have written support in the specification, claims, and/or drawings as originally filed. The specification mentions correlations of samples (i.e. paragraphs 26 and 27), but it does not recite associations which differ in scope. The specification (page 6, line 30) recites the phrase "each sample is isolated and coded"; however, a code differs in scope from an index which is interpreted to be a list. Claims 7 (lines 7-9) and 11 (lines 2, 6, and 8) recite the phrase "first biological tissue sample" which does not appear to have written support in the specification, claims, and/or drawings as originally filed. While the specification mentions characterizing a tissue sample by cutting the sample into first and second sample section sets (see claim 1), it does not mention characterizing a first biological tissue sample. Claim 10 (line 4) recites the phrase "either directly or indirectly" which does not appear to have written support in the specification, claims, and/or drawings as originally filed. Because the introduction of the phrases "associating each incised section sample", "unique set of indices", "associated with the indexed incised section sample", and "either directly or indirectly" do not appear to have adequate written support in the specification, claims, and/or drawings as originally filed, these

phrases are considered to be NEW MATTER. Claims 2-3 and 9-10 are also rejected due to their dependency from instant claims 1 and 7.

Applicant states claim 7 has been amended to remove terms such as "first biological tissue sample". It is noted that some, but not all, of the NEW MATTER phrases have been removed.

Claims Rejected Under 35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 6-7, and 9-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Claims 1 (line 8), 7 (line 6), 9 (line 5), 10 (penultimate line), and 11 (line 6) recite the phrase "based on" which is vague and indefinite. It is unclear what criteria and to what degree these criteria must be met to be considered to be "based on". Clarification of this issue via clearer claim wording is requested. Claims 2-3 are also rejected due to their dependency from claim 1.

Claims 1 (lines 19 and 28) and 4 (line 7 and penultimate line), claim 7 (line 15), and 11 (line 14) recite the term "utilizing" which is vague and indefinite as it recites a use without any active, positive steps delimiting how this use is actually practiced. Clarification of this issue via

clearer claim wording is requested. Claims 2-3, 6, and 9-10 are also rejected due to their dependency from claims 1, 4, and 7.

Claim 4 (line 14) recites the phrase "the serial sample section" which lacks clear antecedent basis as it is unclear if this section is from the first or second set. Clarification of this issue via clearer claim wording is requested. Claim 6 is also rejected due to its dependency from claim 4.

Claims 4 (line 17), 6 (line 2), 7 (penultimate line), 9 (line 4), 10 (line 4), and 11 (penultimate line) recite the terms "corresponding" or "corresponds" which are vague and indefinite. It is unclear what criteria and to what degree these criteria must be met to be considered to be corresponding. Clarification of this issue via clearer claim wording is requested.

Claim 4 (penultimate line) recites the phrase "the index data" which lacks clear antecedent basis as it is unclear if the data referred to are from the providing step or the analyzing step. Clarification of this issue via clearer claim wording is requested. Claim 6 is also rejected due to its dependency from claim 4.

Claim 7 (lines 7-9) recites the phrase "said first biological tissue sample" which lacks clear antecedent basis as it there is no previous mention of this sample. Clarification of this issue via clearer claim wording is requested. Claims 9-10 are also rejected due to their dependency from claim 7.

Claims 9 and 10 recite limitations "each incised section sample" (claim 9) and "each indexed incised section sample" (claim 10); however, these claims are confusing as it is unclear

which steps in instant claim 7 (from which they depend) they are intended to further limit. Clarification of this issue via clearer claim wording is requested.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. (e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heppelmann et al. (Journal of Microscopy, Vol. 156, Pt. 2, 1989, pages 163-172) in view of Cole et al. (Nature Genetics supplement, Vol. 21, 1999, pages 38-41), Farr et al. (P/N 5,811,231), and Emmert-Buck et al. (Science, Vol. 274, 1996, pages 998-1001).

Heppelmann et al. describe methods for creating multidimensional morphological reconstruction of biological tissue data characterizing a biological tissue sample by cutting histologically thin sections of tissue in two sets of alternating serial sample sections (page 163, lines 1-12) as stated in claims 1, 4, 7, and 11. Heppelmann et al. describe performing these three dimensional reconstructions with graphical techniques and computer-aided methods (page 163, lines 13-14) featuring a spatial matrix of image data with x, y, and z axes as seen in Figure 4, which represents mapping image data obtained from the first set of alternating serial sections onto a coordinate system as well as volume image data correspondence, as stated in claims 1, 4, 7, and 9-11. Heppelmann et al. describe cutting the second set of sections (for ultrastructural examination) and mounting them on single-slot grids to be further examined (page 164, last paragraph) which represents creating a grid pattern across each serial sections to create a set of incised section samples for each serial section of the second set, as stated in claims 1, 7, and 11. Heppelmann et al. describe the sections were mounted in sequence on mesh grids (page 165, lines 12-14) which is reasonably interpreted to be associating each incised section sample with unique set of indices as it has grids (x and y coordinates) with each individual sample placed in a known location as stated in claims 1 and 4.

Heppelmann et al. describe histologically-staining the first set of sections and adding a coverslip (page 164, fifth paragraph) which could be used for light microscopy reconstructions (page 163, lines 4-5) as stated in claim 4. Heppelmann et al. describe that the second set of tissue sections are covered with a synthetic membrane which is then further cut (page 164, paragraphs 6 and 7) as stated in claim 4.

Heppelmann et al. do not teach using a microarray and biological data analyses type which involve mRNA as elected in the species elections. Heppelmann et al. do not teach linking these data to each indexed tissue sample in the multidimensional morphological matrix. Heppelmann et al. do not analyze tissue with monoclonal antibodies or obtain gene expression data and superimpose them on the multidimensional morphological matrix of image data to display correlating values of data with corresponding locations on the matrix.

Cole et al. describe a web-based, visual system for allowing querying of gene expression profiles while viewing associated anatomy and histopathology (page 40, col. 2 (third paragraph) which represents a system of creating morphological reconstruction of biological data characterizing a tissue, as stated in instant claim 11. Cole et al. describe a model for integrating three dimensional expression data obtained using a microarray involving mRNA analysis (page 38, abstract (lines 5-6), and col. 1 (lines 1-4)) which represents methods and systems for utilizing biological activity methods to analyze sections providing a plurality of biological characteristics of the indexed samples, as stated in instant claims 1 and 3. Cole et al. discuss cutting tissue in transverse cross-sections (representing X and Y dimensions) available for microdissection and recutting adjacent serial sections in the Z dimension (page 40, col. 1, lines 7-14) which are used to create a multidimensional morphological spatial matrix of image data as seen in Figure 1 which represents incising a grid pattern across each serial section of a set, as stated in instant claims 1, 4, 7, and 11. Cole et al. discuss the placement of tissue on slides (page 40, col. 1, lines 11-12) and other newly developed fixation and embedding strategies (page 39, col. 2, lines 15-16). Cole et al. describe methods of preparing microarrays from microdissected cells (page 40, col. 1, lines 19-25 and 37-39). Cole et al. discuss that the above processes allows for the

determination of exact physical relationships between morphological data (one set) on which to overlay gene expression data (second set)(page 40, col. 1, lines 14-17 and col. 2, lines 16-24) which represent associating indices from each incised section sample of the second set with indices of the morphological tissue space matrix, as well as obtaining and analyzing biological data, and utilizing indices to link data characterizing each sample to the location, as stated in claims 1, 7, and 11. Cole et al. describe viewing this information on computers and displaying a data chart in three dimensions (page 40, col. 2, lines 26-38) which represent spatially mapping the biological data characterizing each indexed incised section sample of the second set onto the multidimensional morphological tissue space matrix from the first set, as stated in claim 1. Cole et al. show images of stained tissue sample sections obtained from light microscopy (Figure 1, molecular view) as stated in claim 4. Cole et al. do not teach superimposing analyzed data on the multidimensional morphological matrix of image data, analyzing tissue with monoclonal antibodies, and correlating data with corresponding locations on the matrix.

Farr et al. describe a method of measuring biological data, particularly as gene expression levels from specific organs of animal tissues to characterize and identify cellular and subcellular effects of potential toxins on an animal cell (col. 2, lines 52-62 and col. 6, lines 15-23). Farr et al. describe starting experiments with tissue sample and cell lines (col. 6, lines 15-23). Farr et al. describe the results graphically in Figures 1-11 (col. 31, lines 5-6) which consist of multidimensional (3D) representations of the biological data. As can be seen in the Figures 1-11, each data column is indexed and to a particular set of conditions, such as the expression of an enzyme under control of different promoters in the presence of varying concentrations of a test compound (col. 3, lines 24-67). Each of these particular set of conditions was tested with genetic

material bound to a solid support membrane which was placed on a 96-well plate (col. 20, lines 53-67; col. 26, lines 9-11; and col. 29, lines 49-51) which allowed for proper indexing and correlation of each set of test conditions to the resulting graphical representations described above as stated in claims 1, 4, and 6. Farr et al. describe an autoradiograph taped to a 96-well plate holder to align the radioactive dots with the holes of the plate holder so that each well is quantified according it each well position (col. 28, lines 23-27) which is a form of image data superimposed and visually transferring of grid elements to the corresponding indexed grid element holder, providing indexed grid holders indicating identity of the sample sections and coordinate location, and analyzing each grid element with expression data, as stated in instant claims 1 and 4. Farr et al. describe correlating the results and creating profiles (col. 28, lines 30-32) as stated in claim 6. Farr et al. describe analyzing assays using antibodies to detect proteins (col. 19, lines 55-67 and col. 20, lines 1-14) with expression levels being regulated by interactions between surface receptors and ligands (col. 4, lines 52-55) as stated in claim 2. Farr et al. describe the method to include detecting levels of mRNA (col. 20, lines 25-67) as stated in claim 3. Farr et al. do not teach physically transferring incised grid elements.

Emmert-Buck et al. describe a film or membrane applied to the surface of a tissue section on a glass slide (abstract, lines 3-5), which represents mounting and covering a second set of sections with a micro dissection membrane, as stated in instant claim 4. Emmert-Buck et al. describe a laser applied to specific locations the film to procure specifically targeted cells that can then be transferred (abstract, lines 5-9) which suggests incising grid patterns of the tissue and selecting only particular subsections.

Cole et al. state that gene expression microarrays hold great promise in studies of human disease states (abstract, line 1). While some technical issues have yet to be addressed, other precise measurement techniques are at hand to view molecular anatomy of normal cells and their disease counterparts (Cole et al., abstract). Farr et al. state the need for quick, inexpensive and reliable alternatives to toxicity testing in animals (col. 2, lines 11-13) such as using techniques of measuring transcription and translation levels of genes (col. 2, lines 52-62). Farr et al. state the kits and methods of their invention yield rapid and direct information about the nature of a compound's action on mammalian cells (col. 3, lines 12-21). Farr et al. also state that the basic construction of the kits, processes, and products of their invention can be altered to provide other embodiments (col. 32, lines 14-21). Heppelmann et al. state that complex morphological structures cannot be fully appreciated without three-dimensional reconstruction (page 163, lines 15-16). Heppelmann et al. point out that stacking of contoured sections for reconstruction is an old technique that is now aided by graphical methods and computers (page 163, lines 16-21). A skilled artisan in the art would have been motivated to improve the methods of representing biological data via direct comparisons of genetic expression and morphological data as stated by Cole et al. (page 40, col. 2, lines 21-28) in order to precisely identify and characterize biological effects on certain tissues as stated by Farr et al. (abstract, lines 1-12). Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to utilize improved methods of comparison of multidimensional graphic data expression representation to microscopy data, as stated by Cole et al. (page 40, col. 2, lines 21-28) via three-dimensional histological techniques to increase understanding of complex morphological structures as stated by Heppelmann et al. (page 163, lines 15-16 and page 171, lines 11-13), using simple and

precision tissue extraction with laser capture microdissection that minimizes contamination, as stated by Emmert-Buck (abstract and page 998, col. 3, lines 2-6 and 12-15), and displaying the gene expression data in easy-to-read three-dimensional graphs as shown by Farr et al. (such as Figure 1), because these exact and efficient techniques would improve accuracy and visual representation for easy interpretation of correlations between the two types of data available to scientists at the time of the invention.

Thus, Heppelmann et al., in view of Cole et al., Farr et al., and Emmert-Buck et al., motivate the instant invention.

Applicants summarize one embodiment of their invention. Applicants argue that Heppelmann et al. describe a re-embedding technique wherein tissue is cut into serial sections and some sections are selected to be re-embedded and converted into a series of thin sections for viewing, wherein further serial section ESI-technique is performed. It is noted that some of these descriptions are found within the limitations of the instant claims. Applicants summarize the Cole et al., Farr et al., and Emmert-Buck et al. references. Applicants argue that the above cited references do not disclose the steps recited in instant claims 1, 4, 7, and 11. This statement is found unpersuasive as the claims were interpreted as broadly and reasonably possible, wherein the limitations of the instant invention are considered to be found in these references. Applicants argue that the steps of incising a grid pattern on a serial section to form a set of incised section samples and assigning indices is not described in any of the references. This statement is found unpersuasive as these limitations are addressed in the rejection above. Applicants state that the term "grid" used by Heppelmann et al. refers to a mesh-like structure of the substrate utilized to

mount the sections and does not assign coordinates to the sections. It is noted that not every limitation must come from a single reference in a 35 USC 103(a) rejection. These terms used by the Applicants can be more broadly and yet reasonably interpreted which includes the mesh-like grid inherently contains a grid pattern with a coordinate spatial matrix. However, the incising a serial section into a grid pattern is also present in the Cole et al. reference. Applicants argue that the Cole et al. reference and Emmert-Buck et al. do not incise a serial section into a grid and assign indices. This statement is found unpersuasive as the instant claims do not recite incising a serial section into a grid, but rather incising a grid pattern across each serial section, which differs significantly from what Applicants are arguing. The broad interpretation of this limitation may be found in the Cole et al. reference with cutting tissue in transverse cross-sections (representing X and Y dimensions) available for microdissection and recutting adjacent serial sections in the Z dimension (page 40, col. 1, lines 7-14). This may not be the grid pattern that Applicants intended, but it is indeed a grid pattern across each serial section. The assigning of indices is reasonably and broadly interpreted to be to consist of any presence of information (list or signal) which is discussed repeatedly in the above mentioned references. Applicants' arguments are deemed unpersuasive.

Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center. The

faxing of such papers must conform to the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR §1.6(d)). The Central Fax Center number for official correspondence is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carolyn Smith, whose telephone number is (571) 272-0721. The examiner can normally be reached Monday through Thursday from 8 A.M. to 6:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner Tina Plunkett whose telephone number is (571) 272-0549 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

June 20, 2005

MARJORIE A. MORAN
PRIMARY EXAMINER

Marjorie A. Moran
6/23/05